PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1932/PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CH2004/000134	International filing date *(day/month/year)* 08.03.2004	Priority date *(day/month/year)* 08.03.2004
International Patent Classification (IPC) or both national classification and IPC INV. A61L24/02		
Applicant STIFTUNG, Robert, Mathys et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.10.2005	30.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fey-Lamprecht, F Telephone No. +49 89 2399-7886

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CH2004/000134

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-59 as originally filed

Claims, Pages

13, 19 received on 04.10.2005 with letter of 30.09.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

   see separate sheet

II. Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☒ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 55

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 55

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-11, 33, 35-36, 48-50,53
	No:	Claims	1-7,12-32,34,37-47,51,52,54,56-59
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-54, 56-59
Industrial applicability (IA)	Yes:	Claims	1-54, 56-59
	No:	Claims	55

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

The amendments filed with the International Bureau under Article 19(1) introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 19(2) PCT. The amendment concerned is the following: "E) said ACP is able to react with water thereby producing a hardened cement; and". No basis for this amendment has been found in the application. The only basis found is the one on p.1 l.4 to 9. However, in this paragraph, calcium phosphate cements are described as hardening cements. No direct basis for the relation between ACP and the water hardening reaction is present in the description.
The amendment part F) find its basis in old claim 49. However no real and unambiguous combination of all new 4 characteristics (C, D, E and F) can be found in the description.
Therefore, the **amendments filed are not taken into account** for the following examination.

Re Item III

No opinion will be given for claim 55 with regard to novelty, inventive step and industrial applicability according to Article 34(4)(a)(I) and Rule 67(1)(iv) PCT, because it is referring to a surgical method of treatment.

Re Item V

Reference is made to the following documents:

D1: US 2003/120351
D2: EP-A-0 639 366
D3: US 2003/199615
D4: US-A-5 782 971
D5: WO 2004/000374
D6: GBURECK U ET AL: "Mechanical activation and cement formation of beta-tricalcium phosphate" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 24, no. 23, October 2003 (2003-10), pages 4123-4131
D7: SERRAJ SIHAM ET AL: "Effect on composition of dry mechanical grinding of calcium phosphate mixtures" JOURNAL OF BIOMEDICAL MATERIALS

RESEARCH, vol. 55, no. 4, 15 June 2001 (2001-06-15), pages 566-575

The relevant passages are cited in the International Search Report.

The following examination is based on the claims 1 to 59 as originally filed with the entry in the PCT Phase on the 08.03.2004.

1. Novelty

The present application is not meeting the requirements of Article 33(2)PCT because the subject-matter of claims 1-7, 12-32, 34, 37-47, 51, 52, 54, 56-59 is not novel.

Independent claims 1, 57 and 59 as well as dependent claim 2 are product claims. However, they are described by a process features. A product can not be rendered novel by the process of manufacture and can only be patentable if the product per se is patentable (novel). See PCT Guidelines 5.26-5.27.

D1 describes a calcium phosphate self-setting cement comprising a calcium phosphate powder and a carrier fluid (aqueous solution). The calcium phosphate powder is obtained by high energy grinding so that an amorphicized calcium phosphate is left. The original calcium phosphate can be tetracalcium phosphate, tricalcium phosphate..., more than one calcium phosphate can be comprised (monocalcium phosphate...).Therefore, D1 is anticipating the subject-matter of claims 1, 2, 4-6, 13-17, 21-23, 26-28, 37-47, 51, 52, 56-59.

D2 describes a cement obtained by a tetracalcium phosphate ground to powder with a high speed ball mill that is known to give an amorphous product. Additionally, the cement can contain amorphous calcium phosphate or monocalcium phosphate monohydrate (see p.3, lines 30 to 35). Therefore, D2 is anticipating the subject-matter of claims 1-4,12,24-28,54,56,57,59. Even, if the first product would not be amorphous since the second calcium phosphate can be an amorphous one, the product D2 would be identical to the one of the present application (see paragraph product by process).

D3 describes a composition for cement comprising a water-based liquid component and a powder component of amorphous calcium phosphates. Additionally, a polysaccharide or

polypeptide or polymer is included in the liquid component and a barium containing calcium phosphate is contained in the powder as well as citrate. A bioactive agent can be found in the cement. Therefore, D3 is anticipating the subject-matter of claims 1-7,12,13, 21-23, 26-28, 30-32, 34, 37-39, 44-47, 56-59.

D4 describes a calcium phosphate cement comprising a dry component of amorphous calcium phosphate having a calcium to phosphate molar ratio of about 1,6 to 1,8 and at least one additional calcium phosphate and a physiologically acceptable aqueous lubricant. The cement can also contain a polymer, a protein, apatite or hydroxyapatite (setting accelerator) and can be replaced by the natural bone. Therefore, D4 is anticipating the subject-matter of claims 1, 2, 4-6, 12-20, 26-28, 44, 46, 47, 56, 57 and 59.

D6 describes cement formation by high-energy ball milling of beta-tricalcium phosphate. The state of the calcium phosphate is then transformed from the crystalline to the amorphous state. The calcium phosphate is milled in ethanol and afterwards mixed with an aqueous solution to become cement. Sodium phosphate is used to accelerate the setting reaction of the cement. Therefore, D6 is anticipating the subject-matter of claims 1-3, 5, 6, 12-15, 24-29, 54, 56, 57 and 59.

D7 describes the preparation of hydraulic calcium phosphate cements by dry grinding tetracalcium phosphate or alpha- beta- tricalcium phosphate and creating anhydrous, noncrystalline calcium phosphate. Different other calcium phosphate can be introduced in the cement. Therefore, D7 is anticipating the subject-matter of claims 1, 2, 4-6, 26, 27, 56, 57 and 59.

2. Inventive step

The present application is not meeting the requirements of Article 33(3)PCT because the subject-matter of claims 1-54 and 56-59 is not involving an inventive step.

The closest prior art is D5 in which a hydraulic cement based on calcium phosphate for surgical use is made. The cement comprises a first component of alpha-tricalcium phosphate powder particles and a second component comprising water. Additionally, the cement contain calcium sulphate dihydrate.
The difference with the present application is the use of calcium triphosphate and not of an

amorphous calcium phosphate.
The problem to be solved is "how to provide an alternative cement".
The solution is to use another calcium phosphate. Since amorphous activated calcium phosphates are known to ameliorate the properties of the cement (setting time decreases, specific area increases) see D6, D7 and D1, the skilled man in the art would consider it as obvious to combine the amorphous calcium phosphate of D1, D6 or D7 with D5. Since the dependent claims of D5 and of the present application are nearly identical, none of the claims 1 to 54 and 56 to 59 of the present application is presenting an inventive step in the sense of Article 33(3) PCT.

Re Item VIII

The application does not meet the requirements of Article 6 PCT, because claims 26, 37, 38, 42, 43, 47, 48 are not clear. These claims are mentioning three components, however the hydraulic cement of the present application comprises in claim 1 two components. Therefore, claims 26, 37, 38, 42, 43, 47, 48 are not meeting the requirements of Article 6 PCT. For the rest of the examination they will be interpreted as comprising two components and if an additives or something is in the "third" component it will be understood as being in the second component.

CLAIMS 2112/PCT (23.3.2005)

1. A hydraulic cement based on calcium phosphate for surgical use comprising

A) a first component comprising powder particles of calcium phosphate; and

B) a second component comprising water,

characterized in that

C) said calcium phosphate comprises anhydrous, amorphous calcium phosphate (ACP);

D) said ACP is obtained by milling a calcium phosphate synthesized above 500°C;

E) said ACP is able to react with water thereby producing a hardened cement; and

F) the specific surface area (SSA) of the powder particles of said first component is in the range of 0,05 to 10,00 m^2/g.

2. A hydraulic cement according to claim 1, characterized in that said ACP is obtained by milling of one or more substances chosen from the group of

a) α-tricalcium phosphate [(α-TCP; $Ca_3(PO_4)_2$] ;

b) β-tricalcium phosphate [(β-TCP; $Ca_3(PO_4)_2$] ;

c) oxyapatite [(OXA); $Ca_{10}(PO_4)_6O$];

d) tetracalciumphosphate [TetCP; $Ca_4(PO_4)_2O$]

in the presence of not more than 20 weight percent of a non-aqueous auxiliary milling liquid compared to 100 weight percent of calcium phosphate.

3. Cement according to claim 2, characterized that the auxiliary milling solvent is an alcohol, preferably ethanol, or isopropanol.

4. Cement according to one of the claims 1 to 3, characterized in that additionally to said ACP it contains one or several other calcium phosphates from the following list: monocalcium phosphate (MCP; $Ca(H_2PO_4)_2$); monocalcium phosphate monohydrate (MCPM; $Ca(H_2PO_4)_2.H_2O$), dicalcium phosphate (DCP; $CaHPO_4$), dicalcium phosphate dihydrate (DCPD; $CaHPO_4.2H_2O$); Octocalcium phosphate (OCP; $Ca_8H_2(PO_4)6.5H_2O$); calcium deficient hydroxyapatite (CDHA; $Ca_9(HPO_4)(PO_4)_5OH$), hydroxyapatite (HA; $Ca_{10}(PO_4)_6(OH)_2$), beta-tricalcium phosphate (β-CP; $Ca_3(PO_4)_2$), oxyapatite (OXA; $Ca_{10}(PO_4)_6O$), tetracalcium phosphate [TTCP; $Ca_4(PO_4)_2O$] and α-tricalcium phosphate.

lanolin [CAS registry number 8020-84-6], lecithin [CAS registry number 8002-43-5], medium chain triglycerides (no registry number), monoethanolamine (C_2H_7NO), oleic acid ($C_{17}H_{33}COOH$), polyethylene glycol monocetyl ether [CAS registry number 9004-95-9], polyethylene glycol monostearyl ether [CAS registry number 9005-00-9], polyethylene glycol monolauryl ether [CAS registry number 9002-92-0], polyethylene glycol monooleyl ether [CAS registry number 9004-98-2], polyethoxylated castor oil [CAS registry number 61791-12-6], polyoxyl 40 stearate ($C_{98}H_{196}O_{42}$), polyoxyl 50 stearate ($C_{118}H_{236}O_{52}$), triethanolamine ($C_6H_{15}NO_3$), anionic emulsifying wax [CAS registry number 8014-38-8], nonionic emulsifying wax [CAS registry number 977069-99-0], and sodium dodecyl sulfate ($NaC_{12}H_{25}SO_4$).

49. Cement according to one of the claims 1 to 48, characterized in that the specific surface area (SSA) of the first component is in the range of 1.5 to 3.5 m^2/g"

50. Cement according to one of the claims 1 to 49, characterized in that the cement viscosity of the cement is larger than 1Pa·s at a shear rate of 400 s^{-1}, one minute after the start of cement mixing.

51. Cement according to claim 50, characterized in that the cement viscosity of the cement is larger than 10Pa·s at a shear rate of 400 s^{-1}, one minute after the start of cement mixing.

52. Cement according to claim 51, characterized in that the cement viscosity of the cement is larger than 100 Pa·s at a shear rate of 400 s^{-1}, one minute after the start of cement mixing.

53. Cement according to claim 52, characterized in that component "a)" additionally comprises water-soluble phosphate salts and component "b)" comprises a polymer, preferably sodium hyaluronate

54. Cement according to one of the claims 1 to 53, characterized in that the setting time of the mixture of said two components is between 2 to 15 minutes, preferably between 5 and 12 minutes.